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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/614,326	07/12/00	EDELBERG J	0050.1609-00

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EXAMINER	
DHRUVA, B	
ART UNIT	**PAPER NUMBER**
1632	6

DATE MAILED: 05/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/614,326	EDELBERG ET AL.	
	Examiner	Art Unit	
	Bharati R. Dhruva	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 26-71 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 26-71 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Claim Objections

Claims 33, 34 and 46,47 are objected to because of the following informalities: The claims depend on already canceled claims.

Claim 33 depends on claim 7, which was cancelled in preliminary amendment filed on 03/06/01. Claim 46 depends on claim 20 which, which was cancelled in preliminary amendment filed on 03/06/01. Furthermore, claims 34 and 47 respectively, depend on 33 and 46 are also objected for their dependency on cancelled claims.

For examination purpose, claim 33 is taken as being depend on 32 and 46 being dependent on 45.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 recites the limitation "...cell is isogenic,allogenic or xenogenic" in claim 31. There is insufficient antecedent basis for this limitation in the claim. Claim 31 only recites the group of genes; β_2AR,β_1AR and Gαs and does not refer to any cell types.

Claims 38,51 and 63 recites the limitation "agonist is isoproterenol" in claims 36, 49 and 61 respectively. There is insufficient antecedent basis for this limitation in the claim. Claims 36,49 and 61 recites method of introduction of biological pacemaker by injection, transfection or transduction, it does not mention administering an agonist.

Claim 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 48 recites " A method of improving cardiac function" but is does not define what is the meaning of improvement and improvement over what. At what percentage level over the initial condition the improvement is considered as improvement. The claim lacks process steps which relate to the preamble.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the expression of the β_2AR gene in *in vitro* in myocardiac by transfection of the construct and being enabling for increase rate of contraction in the transduced cells does not reasonably provide enablement for *in vivo* correction of the cardiac dysfunction in mammals, specifically in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of introducing a biological or molecular-mediated pacemaker by direct injection or transfection and transduction into atrail chamber or sinoatrial node region of a mammalian heart for improving cardiac function in senescent or in dysfunctional heart. The claims are further drawn to method of treatment by transient expression of molecularly mediated cardiac pacemaker and permanently regulating cardiac pacemaker activity by cellular based and by molecularly based cardiac pacemaker. The specification discloses that the biological pacemaker of the instant invention could be useful for the treatment of individual suffering from cardiac conductive tissue incompetence and in older patients with clinical conditions (pp.4 lines 16-21, pp.15 lines 23-29). Thus, in light of claims and specification there is no disclosed use of the invention but for a therapeutic outcome.

Gene therapy *in vivo* continues to be unpredictable and inefficient. This fact is supported by various teachings available in the art at the time of filing. Verma and Somia (Nature 1997, Vol. 389 page 239-242) review various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention the inability to deliver gene efficiently and to obtain sustained expression are a major hurdle (page 239 para. 5 lines 3-6). In their recent review Somia and Verma (Nature Reviews 2000; Vol. 1 page 94 para 6 and page 95 para 1) discuss the role of the immune system in inhibiting the efficient gene delivery using viral vector. In a recent review, Hajjar et al. (Circulation Research, 2000, Vol.86,pp.616-621) defined three essential elements for the clinical success of gene therapy; a vector which has high efficiency of delivery of transgene, expression of

transgene in postmitotic cells such as cardiomyocytes, and the delivery of the vector to the affected tissue and the appropriate gene to be expressed in a particular clinical setting. Hajjar et al. further state, "However it is important to acknowledge that the field of gene therapy has yet not proven its clinical value in any context (pp.617, para.2 lines 19-21)". Alexander et al. (1999, Clinical and Experimental Pharmacology and Physiology, vol.26,pp.661-668) state that both direct gene transfer and cell grafting have limitation in cardiac gene therapy(pp.666, para.4 line,) as only a small number of cells at the site of injection express the transgene (pp.662, para.5. lines 1-3, pp.66, para.4, lines) and viral vectors lead to the inflammatory response and eventual shut off of the transgene expression. They further discuss that long term expression in neonatal cardiomyocytes but not in adult mice (pp.664, para.3, lines 4-8, 10-11) were obtained with intravenous injection of an adeno vector. Furthermore, Alexander et al. state that, " Allogenic and xenogenic myoblasts injected into the anterior and posterior walls of the porcine left ventricle were successfully transplanted in immunosuppressed animals with no significant graft rejection. No reports have yet claimed to show changes in myocardial function in response to cellular transplantation (pp.665,para.5,lines 8-13)" Drazner et al. (Proc. Assoc. Am. Physician, 1997, Vol.109,pp.220-227) in the article conclude that " It is not possible to know the full consequences of cardiac over expression of specific components of βAR signaling cascade a priori. Because the over expression of β_2Ars, Gsα or a βARK inhibitor can enhance cardiac function beyond the normal physiological state, it is likely that such strategies could improve the inotropy of a failing myocardium. However, as these three strategies have fundamentally different

mechanism of action, it is possible that they may lead to different hemodynamic consequences and outcomes in survival when applied to animal models of CHF."

Thus, at the time of the filing of the instant application, the state of the art was replete with evidence that methods of *in vivo* delivery and successful gene expression were not predictable without undue amount of experimentation. Furthermore it was also observed that successful grafting of cells in myocardial tissue did not lead to a change in myocardial function.

The specification describes higher rate of contraction (pp.23 lines, 24-26) and chronotropic rates (pp.23 lines 12-16) *in vitro* myocyte transfected with β_2AR under the control of β actin promoter and linked to SV40 polyA signal, (pp.21 lines 17-20). Increased heart rates in the β_2AR construct injected into neonatal murine heart, transplanted into ear pocket (pp.24, lines 9-14, 27-28) were also observed (Fig.3). The specification also describe increased β_2AR in the right atrium (pp.26, lines 23-26) and increased contraction rates (Fig.4A, pp.27 lines 5-8) of a six week old murine heart injected with the β_2AR expression vector. The specification further teaches injection of β_2AR construct in a pig heart (pp.28, lines 25-pp.29 cont.) and demonstrates increased heart rates (pp.31 lines 8-13).

It is evident from the applicant's claim and specification that the usefulness of the claimed invention is to express the transgene for a therapeutic outcome. The only disclosed use is for the *in vivo* gene delivery is to improve cardiac dysfunction in a patient. The specification taken as a whole, including both discussion and specific

examples and the prior art provide insufficient guidance to a skilled artisan to reach an effective therapeutic outcome by implementing claims 33-71.

The specification describes β_2AR expression and increased in contractile rates in *in vitro* cultured myocytes and β_2AR expression and increased heart rates *in vivo* heart or transplanted heart. Though the claims recite "improving cardiac dysfunction" and "regulating cardiac pacemaker activity" the applicants have not shown any working example of the improvement of cardiac dysfunction in diseased heart or improvement of cardiac function in senescent heart. The specification only demonstrates the increase in β_2 andrenergic receptor and increase heart rates in healthy heart and healthy myocytes in culture. Furthermore, it is not clear how the increase in heart rate would improve cardiac function, for example in arrhythmia, which is irregular heart beat or in case of cardiac hypertrophy, which is developed in response to increased B andrenergic signaling leading to increase in mass and size of the heart. It is unclear how increasing heart rate would provide a therapeutic effect to these or other myocardial dysfunction. Applicants have not disclose any data demonstrating improvement or regulation of a senescence or dysfunctional heart. Furthermore the specification does not provide guidance to the dosage amount, dosage frequencies, the expression levels and any other routes than the direct injection for *in vivo* targeted delivery of a plasmid vector for improvement in cardiac function.

In view of the unpredictability of gene transformation *in vivo* discussed earlier, lack of success so far in *in vivo* gene therapy or cellular based therapy as noted by Alexander et al, the unpredictable consequences and outcomes of the over expression

of the β_2AR genes as stated by Drazner et al., the lack of guidance in the specification, and the breadth of the claims it would require undue experimentation for one skilled in the art to implement the invention as claimed.

There is no evidence that the claimed invention would improve the cardiac function in a senescent heart or correct rhythm in a dysfunctional heart. Hence, the specification is enabling only for claims limited to *in vitro* transfection of cells with β_2AR gene, β_1AR gene, and Gαs gene with or without agonist.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26,28-29, 31, 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Milano et al. (Science, 1994, Vol. 264, pp.582-586).

Claims 26,28-31and 43 are drawn to a molecularly-mediated cardiac pacemaker construct suitable for localized gene expression in mammalian cardiac atrial tissue, comprising a gene selected from the group consisting of, β_2 adrenergic receptor (β_2AR), β_1 adrenergic receptor (β_1AR) and Gsα for unregulated heart rate. Furthermore the claims recite the construct comprises a control elements which directs stable expression.

Milano et al. teach a construct comprising murine α myosin heavy chain promoter (αMHC) β_2AR gene and part of SV-40 intron in 3' untranslated region (pp.583, para 1,

lines 1-5 , 27-30) which is stably expressed in murine heart (para.5, lines 4-7) and upregulated the heart rate (page 584, Fig. 5 C). Milano et al. further states that their studies demonstrate the potential of genetic engineering as a modality for enhancing myocardial and ventricular function.

Thus the instant application encompass the same embodiments as that of Milano et al. Thus Milano et al. anticipate the claim invention.

Claims 26,28-31 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Gaudin et al.(Journal of clinical Investigation, 1995, Vol. 95,pp.1676-1683)

Claims 26,28-31and 43 are drawn to a molecularly-mediated cardiac pacemaker construct suitable for localized gene expression in mammalian cardiac atrial tissue, comprising a gene selected from the group consisting of, β_2 adrenergic receptor (β_2AR), β_1 adrenergic receptor (β_1AR) and Gsα for unregulated heart rate. Furthermore the claims recite the construct comprises a control elements which directs stable expression.

Gaudin et al. teach a construct comprising Gsα, a heterodimeric guanine nucleotide binding stimulatory protein, capable of expressing in cardiac tissue, controlled by a α MHC promoter (pp. 1676, para2. complete and fig.1). They further demonstrate accelerated activation of adenylyl cyclase activity in transgenic mice expressing increasing level of Gαs protein (pp.1682 para 5, lines 14-16). They further assess that the relatively small changes in the content of Gsα can impact on receptor-Gs coupling and the rate of adenylyl cyclase activation in the heart.

Thus the instant application encompass the same embodiments as that of Gaudin et al. Thus Gaudin et al. anticipate the claim invention.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 26, 28-31, and 43 rejected under 35 U.S.C. 102(a) as being anticipated by Drazner et al. (J.Clin.Invest.1997, Vol. 99, pp.288-296).

Claims 26,28-31 are drawn to a molecularly-mediated cardiac pacemaker construct suitable for localized gene expression in mammalian cardiac atrial tissue, comprising a gene selected from the group consisting of, β_2 adrenergic receptor (β_2AR), β_1 adrenergic receptor (β_1AR) and Gsα for unregulated heart rate.

Drazner et al. teach transduction of cultured myoblast (pp.289, para.3, lines 1-5) by an adenovirus construct comprising β_2AR gene linked at 5' to CMV promoter and at 3' to bovine growth hormone poly A signal (bGH) (pp.289, para1. Lines 5-8). Furthermore, Drazner et al. demonstrate that the expression β_2AR or βARKct gene increased cAMP (Fig. 4), indicating potentiaion of β andrenergic signaling.

Thus the instant application encompass the same embodiments as that of Drazner et al. Thus Drazner et al. anticipate the claim invention.

Claims 33-71 are free of art. However the claims are rejected under first paragraph of 35 U.S.C. 112.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bharati R. Dhruva whose telephone number is (703) - 605-1157. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached on (703)-305-6608. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and for After Final communications.

Question of formal matters can be directed to the patent analyst Pasty Zimmerman, whose phone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)-308-0196.

Karen M. Hauda

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